Diabetic Foot Infections in the Emergency Department

Bradley W. Frazee, MD*

KEYWORDS

• Diabetic foot infection • Diabetic foot ulcer • Peripheral arterial disease
• Osteomyelitis • Necrotizing soft tissue infection

KEY POINTS

- Remove bandages to examine the foot carefully.
- Routinely obtain plain x-rays.
- Consult guidelines for proper infection categorization and antimicrobial selection.
- Debridement is frequently required.
- Immediate consultation or close follow-up with a foot surgeon is mandatory.

INTRODUCTION

Among the most common diabetic complications encountered in the emergency department (ED), diabetic foot infections (DFIs) account for billions of annual health care spending in the United States and can lead to extremity amputation and near-term death. It is therefore essential that emergency providers be well acquainted with the topic of DFI, as well as the closely associated problems diabetic peripheral neuropathy, peripheral arterial disease (PAD), diabetic foot ulcer (DFU), and osteomyelitis. Providers need to be able to gauge infection severity, order and interpret initial diagnostic tests, select appropriate empiric antimicrobial therapy, decide on appropriate disposition, and recognize when emergent surgical intervention is required. Recent DFI guidelines provide detailed, evidence-based diagnostic and management recommendations. This article offers a review geared specifically for the emergency provider, including how to perform a nuanced diagnostic evaluation and provide state-of-the-art initial management.

EPIDEMIOLOGY

DFUs and DFI are among the most common diabetic complications requiring admission from the ED. Together, these diabetic foot diseases account for 2% of ED visits by

Department of Emergency Medicine, Alameda Health System, Wilma Chan Highland Hospital, 1411 East 31st Street, Oakland, CA 94602, USA
* Corresponding author.
E-mail address: bradf_98@yahoo.com

Emerg Med Clin N Am 42 (2024) 267–285
https://doi.org/10.1016/j.emc.2024.01.003 **emed.theclinics.com**
0733-8627/24/© 2024 Elsevier Inc. All rights reserved.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

SHOUT
SHARE
IT

patients with diabetes, with about 80% requiring admission.[1] There exists a striking link among DFU, associated DFI, the need for amputation, and near-term mortality. The annual foot ulcer incidence among US diabetics is 6%, with roughly 50% of DFUs resulting in DFI.[2] Following a DFI, the 1 year risk of minor or major amputation is 17% to 36%.[3,4] And following DFI-related amputation, 5 year mortality is 52%, on par with many malignancies.[5] These statistics indicate that any ED patient with a DFU, DFI, or history of lower extremity amputation should be considered at very high risk. Additionally, there are significant disparities in DFI-related outcomes along socioeconomic and racial lines, with higher rates of amputation and associated mortality in Black and Latino patients and among patients with low socioeconomic status and from rural communities.[1,4] Finally, the annual US health care costs attributable just to those DFIs that are admitted through the ED sums to 8.78 billion.[1]

PATHOPHYSIOLOGY AND NATURAL HISTORY

Though DFIs—typically superficial abscesses and cellulitis—can develop in the setting of traumatic foot wounds, fungal infection, or venous stasis dermatitis, the majority of severe DFIs develop as a complication of a DFU. Hence, risk factors for, and pathophysiology of, DFUs are closely tied to those of DFI. Diabetic peripheral neuropathy is considered the essential permissive process underlying DFU and DFI: sensory neuropathy causes loss of protective sensation; motor neuropathy can lead to foot deformity and biomechanical abnormalities; autonomic neuropathy causes decreased sweating and dry, cracked skin. Repetitive vertical and shear stress leads to skin breakdown, which often goes unnoticed, and ulcer formation. Once an ulcer forms, healing is often slow and problematic, with infection supervening before skin closure can occur. Factors adversely affecting healing include PAD, large size (>1 cm^2) and location on the heal. Only about 50% of DFUs heal by 1 year, and thereafter, recurrence occurs at a rate of about 40% per year.[2,3]

The surface of chronic DFUs often become colonized with one or more pathogenic bacteria, which then can lead to clinical infection (see “Microbiology” section). New, sophisticated microscopic and molecular techniques have revealed an extensive microbiome in most DFUs, with high bioburden impairing ulcer healing. Infection is often associated with biofilms containing multiple species, which impair antibiotic penetration and are associated with antibiotic resistance.[6,7] Once clinical infection supervenes, hyperglycemia impairs neutrophil function and the avascular articular cartilage, tendons and the many compartments of the foot promote proximal spread of infection. PAD is an important risk factor for DFI development, in part, by slowing the ulcer healing process. PAD is found in 12% of patients with DFUs, but up to 49% of those presenting with DFI.[3,8]

Osteomyelitis complicates about 20% of DFIs and a much higher proportion of those serious enough to require hospitalization.[9] Ulcers and DFIs that occur on bony prominences bring their bacteriologic milieu very close to bone surface. Periosteum is largely avascular, and diabetic microvascular impairment and PAD further disrupt blood flow to the vulnerable bone. Infection and inflammation compress and obliterate vascular channels within bone. Bone devoid of blood supply can separate, forming sequestra, a safe harbor for bacteria not reached by systemic antibiotics.[10]

MICROBIOLOGY

Data on the microbiology of DFIs comes mostly from studies of nonhealing DFUs, osteomyelitis, and severe DFIs requiring hospitalization. Therefore, polymicrobial infection may be overrepresented in the literature, while nonsevere infections such

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

as small abscesses and nonpurulent cellulitis may often be monomicrobial. Aerobic gram-positive pathogens—primarily *Staphylococcus aureus* and beta-hemolytic streptococci—are the most common class of bacterial isolates in DFI studies from the United States and Europe and are even more common in minor infections and in patients not recently treated with antibiotics.[11,12] *S aureus* is the single most frequently isolated pathogen, with methicillin-resistant *S. aureus* (MRSA) accounting for 18% to 30% of these, or about 11% of DFIs overall.[13–15] Therefore, whether or not to include MRSA coverage is a very important consideration in empiric antibiotic selection.

Polymicrobial infection and isolation of aerobic gram-negative and obligate anaerobic species occurs in 10% to 50% of infections and positively correlates with size, depth, and chronicity of the associated ulcer.[6,16–19] Additionally, recent antibiotic therapy is considered an important risk factor for resistant infections. Multidrug-resistant (MDR) gram negatives including *Pseudomonas* and extended-spectrum beta lactamase (ESBL)-producing Enterobacterales species have been common in studies conducted since 2000 in tropical and subtropical countries.[20–22] *Pseudomonas*, in particular, is considered to be more common in the following settings: recent broad-spectrum antibiotic exposure, when the ulcer is macerated or there has been chronic exposure to moisture, or when it has been isolated recently in culture.[12] Obligate anaerobes, such as *Bacteroides* species and *Peptostreptococcus*, are more commonly isolated in the setting of ischemic and necrotic wounds or a fetid odor.[23] Less pathogenic bacteria, including coagulase-negative *Staphylococcus*, Enterococci, and Corynebacteria are frequently isolated in DFIs but of unclear pathogenicity.[12,14]

CLINICAL FEATURES

Owing to underlying sensory neuropathy, patients with diabetes may be unaware that they have a foot ulcer or foot infection. Occult DFI is a notorious cause of sudden worsening of glycemic control. Therefore, careful inspection of the feet is mandatory in patients with diabetes presenting to the ED with foot pain, unexplained hyperglycemia, or systemic signs of infection. Socks and bandages must be removed. A well-lit examination should assess for the following: underlying sensory neuropathy and PAD; presence of an ulcer; signs of infection, and, if present, infection severity; and evidence of associated osteomyelitis. The physical examination alone can confirm or exclude DFI in most cases.

Neuropathy and Peripheral Arterial Disease

Examination for evidence of sensory neuropathy (loss of protective sensation) is considered a standard component of the diabetic foot examination. Assessing for loss of vibration sense on the dorsum of the great toe, with a 128 Hz tuning fork, or loss of light touch, with a 10 g monofilament, are rapid and well-established bedside tests for neuropathy. The Ipswich touch test is a simple alternative that requires no special equipment and performs well. To perform the test, the tips of digits 1, 3, and 5 on both feet are lightly touched for 1 to 2 seconds with the index finger. Failure to feel 2 or more toes being touched constitutes a positive test.[24]

Presence of PAD is another key component of the diabetic foot examination, although it is often overlooked, even in patients admitted for DFI.[25] PAD is the most significant predictor of delayed DFU healing and future amputation, and the presence of PAD indicates that revascularization may be required for successful ulcer healing and DFI treatment. Moreover, PAD, like neuropathy, is 1 of 6 elements of DFU classification (see later discussion). Clinical signs of PAD include a history of claudication

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

and skin that is bluish, hairless, thin, and cool. Absence of pedal pulses is further evidence of PAD, with the absence of both the posterior tibial and dorsalis pedis pulses required for diagnosis. Since clinical signs and pulse palpation may not be accurate, measurement of the arterial brachial index (ABI) is recommended to confirm the impression of PAD, with an ABI of less than 0.9 considered to be confirmatory. Ischemic necrosis ("dry gangrene") due to severe PAD (Fig. 1), may be difficult to distinguish from infectious necrosis ("wet gangrene"), discussed further in a later section.

Diabetic Foot Ulcer

When a foot ulcer is detected on examination, the emergency provider may be asked to describe or classify the ulcer. Guidelines recommend using the Site, Ischemia, Neuropathy, Bacterial infection, Area, Depth (SINBAD) score for classification and to facilitate communication between providers[26,27] (Table 1). Measure and record the area, if possible uploading a photograph that includes a ruler into the medical record. An ulcer with average diameter greater than 1 cm (area >1 cm^2) is considered high risk in the SINBAD score and ulcers greater than 3 cm^2 take a median of just over 1 year to heal[28] (Fig. 2). Assess and record depth with the aid of bright light and an instrument to clear away exudate and devitalized tissue. Depth is graded by the tissue layers penetrated or visible at the ulcer base, as follows: involving skin and subcutaneous tissue only; reaching muscle, tendon, or joint capsule; bone visible or palpable. Ulcers that extend beyond subcutaneous tissue take a median of just over 1 year to heal.[28]

Diabetic Foot Infection and Severity Classification

Diagnosis of DFI generally requires the presence of clearly purulent secretions or 2 or more of the following: increased pain, erythema, induration, warmth, or tenderness (Fig. 3). Additional signs that an ulcer may be infected include the following: foul odor, friable, discolored granulation tissue, undermining of the wound edge[29] (Fig. 4). DFI severity should be classified according to the International Working Group on Diabetic Foot/Infectious Disease of America (IWGDF/IDSA) scheme (Table 2). This classification system is used to tailor empiric antibiotic selection to infection severity, as well as promote consistent communication with consultants and downstream providers.

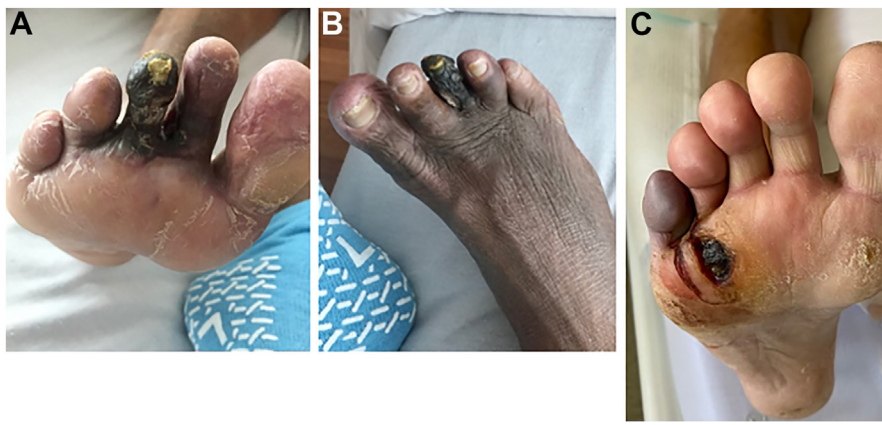

Fig. 1. Peripheral arterial disease. (*A, B*) Ischemic necrosis of the third toe showing "mummification." (*C*) Ischemic necrosis of the fifth toe associated with a nonhealing plantar ulcer. (Photos courtesy of Elly Huang, DPM.)

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 1
SINBAD diabetic foot ulcer severity score[27]

Category	Definition	SINBAD Score
Site	Forefoot	0
	Midfoot or hindfoot	1
Ischemia	Blood flow intact (at least 1 palpable pedal pulse)	0
	Evidence of reduced blood flow (no palpable pedal pulse)	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area	Ulcer <1 cm^2	0
	Ulcer >1 cm^2	1
Total possible score		6

Abbreviation: Site, Ischemia, Neuropathy, Bacterial infection, Area, Depth.

A critical goal of the physical examination in DFI is to detect signs of a rapidly progressive limb-threatening necrotizing soft tissue infection (NSTI). While an NSTI can occasionally be occult or resemble a simple DFI, emergency providers must be alert to, and take seriously, any so-called hard physical examination signs of NSTI. These include necrosis, hemorrhagic bullae, crepitus, discoloration (greyish, purple, and black; Fig. 5). In the diabetic population, where chronic PAD is also common, it may be difficult to differentiate ischemic necrosis ("dry gangrene") from an NSTI due to infection ("wet gangrene"). We recommend that signs of necrosis be considered to be due to infection until proven otherwise.

Osteomyelitis

Physical examination signs that increase the likelihood of underlying osteomyelitis are foot ulcer area greater than 2 cm^2 and the presence of exposed bone.[30] Fever is uncommon in isolated osteomyelitis of the foot.[30] The probe to bone test is a well studied and widely accepted bedside maneuver to test for occult exposed bone in the base of a foot ulcer or wound. The test is properly performed with a sterile blunt metal probe; if

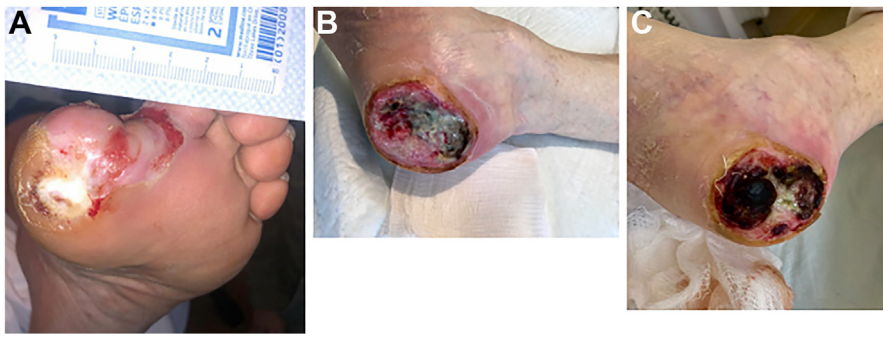

Fig. 2. Diabetic foot ulcers. (*A*) Broad, shallow ulcer associated with prior amputation. (*B, C*) Large, deep undermined foot ulcer showing minor purulent exudate and undermined edges and demonstrating very slow healing. (Photos courtesy of Elly Huang, DPM.)

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

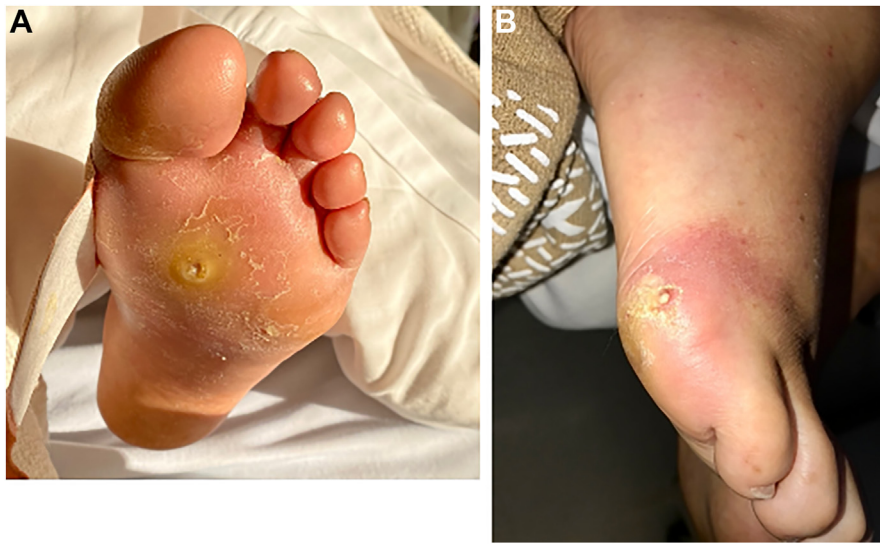

Fig. 3. Minor (class 2) DFIs. (*A*) Small plantar foot ulcer with nonpurulent cellulitis. (*B*) Small ulcer or abscess over metatarsal head with purulence. (Photos courtesy of Elly Huang DPM.)

a probe is not available, a closed Kelly clamp or the wooden end of a sterile cotton-tipped applicator can be used. Feeling a hard, gritty surface constitutes a positive test. The test is typically performed in conjunction with a plain x-ray (see later discussion). In a meta-analysis, pooled sensitivity and specificity of the probe to bone test were 0.9 and 0.8, respectively. However, posttest probability of osteomyelitis will depend on pretest likelihood, which is estimated based on features such as size and chronicity of the associated ulcer and x-ray results.

Differential Diagnosis

A list of other processes that can cause lower extremity pain and inflammation in a patient with diabetes are listed in **Table 3**. Occult fracture (lacking a clear history of trauma) is perhaps the most frequent infection mimic, underscoring the importance of routine x-rays. Otherwise, it is usually possible to distinguish DFI from other causes of foot and leg symptoms without the need for advanced diagnostic tests. Duplex sonography may be needed if deep venous thrombosis is a significant concern.

DIAGNOSTIC TESTS

Imaging

If a DFI is suspected on examination, plain x-rays should generally be obtained to assess for fracture, radio-opaque foreign body, signs of osteomyelitis, and soft tissue gas (beyond that in the ulcer tract), which indicates a possible NSTI (**Fig. 6**). Contrast-enhanced CT is considered the test of choice to further evaluate for NSTI; in the setting of DFI, this modality should be strongly considered when infection extends proximal to the ankle. Diagnostic findings include gas adjacent to fascia, fascial edema, and fascial enhancement.[31]

Plain x-ray signs of osteomyelitis include cortical erosion, periosteal new bone formation, focal medullary osteopenia, bone destruction, and sequestrum (devitalized separated bone).[30,32] Focal findings will typically occur near the base of the ulcer tract

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Fig. 4. Moderate or severe (class 3 or 4) DFIs. (Exact categorization depends on presence of systemic signs.) (*A*) Small ulcer over metatarsal head with purulent drainage and cellulitis. (*B*) Infection, abscess, and localized necrosis over calcaneus. (*C*) Infected ulcer with associated necrosis and cellulitis. (*D*) Deep chronic midfoot ulcer; with pressure, purulence and gas could be expressed the distal portion. (Photos [*A–C*] courtesy of Elly Huang, DPM.)

or in conjunction with soft tissue swelling (see **Fig. 6**). X-ray changes take 2 to 3 weeks to occur. A systematic review of plain x-ray alone to diagnose osteomyelitis reported summary positive and negative LRs for of 2.3 and 0.63, indicating that x-ray is somewhat more useful when positive than negative.[30] Current guidelines recommend that when x-rays are positive and consistent with clinical and laboratory findings, no further imaging is usually needed to confirm osteomyelitis.[12] When needed, MRI is generally

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 2
IWGDF/IDSA diabetic foot infection classification[12]

Uninfected (class 1) foot ulcer	No local or systemic signs of infection
Infected	2 or more of the following local signs: Local swelling or induration Erythema >0.5 cm or > 0.5 cm from wound Local pain or tenderness Local increased warmth Purulent drainage No other cause of local inflammatory response (eg, fracture)
Mild infection (class 2) DFI	Involves skin and subcutaneous tissue only (no deeper tissue) Erythema extends ≤2 cm from wound No systemic manifestations (see later discussion)
Moderate (class 3) DFI	Involves deeper tissue (tendon, muscle, joint, bone) involved, or Erythema extends >2 cm from wound No systemic manifestations
Severe (class 4) DFI	Systemic manifestations present; 2 or more of the following systemic inflammatory response signs: T > 38°C or < 36°C HR > 90 RR > 20 or $Paco_2$ < 32 mm Hg WBC >12,000/mm^3 or < 4000/mm^3 Bands!
Osteomyelitis (add "O" to class 2–4)	Infection involves bone

Abbreviation: International Working Group on Diabetic Foot/Infectious Disease of America.

considered the advanced imaging study of choice to further evaluate for osteomyelitis.[31] In a 2017 meta-analysis, the summary sensitivity and specificity of MRI for osteomyelitis were 93% and 75%, respectively, with specificity limited by the fact that reactive marrow edema can also occur with trauma or Charcot neuroarthropathy.[12,33] Nuclear medicine imaging modalities that can be used to diagnose osteomyelitis include labeled white blood cell (WBC) scintigraphy and flourine-18 flouro-D-glucose positron emission tomography /computed tomography (18F-FDG-PET/CT) scanning, but rarely if ever would these imaging modalities be ordered by an emergency provider.[33]

Inflammatory Markers

Guidelines and reviews emphasize that the assessment of whether a foot ulcer is infected, and infection severity, should be based primarily on physical examination findings. Inflammatory markers play a greater role in identifying osteomyelitis (see later discussion). Nonetheless, inflammatory markers have been studied both for their ability to distinguish infected from uninfected foot ulcers and their correlation with DFI outcomes. While the primary literature consists only of small studies which use different test cutoff values, recent systematic reviews concluded that WBC count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and procalcitonin all perform similarly, with generally limited ability to distinguish an uninfected foot ulcer from infection.[34,35] A normal WBC occurs in 56% of DFIs; therefore, it is not reliable to identify whether an ulcer is infected.[34,36] Nonetheless, WBC should be obtained routinely when evaluating DFI severity, since it is a component of the IWGDF/IDSA DFI classification scheme, in that WBC greater than 12,000 mm^3, less than 4000 mm^3 or bands greater than 10%

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Fig. 5. Diabetic NSTIs of the foot. (*A, B*) Dusky appearance extending from plantar to dorsal surface of the distal foot and toes 2 to 4, which proved grossly infected and devitalized on operative debridement. (*C*) Ischemic and superimposed infected necrosis, with infection extending to the knee, requiring below knee amputation; Fig. 6A shows associated plane x-ray. (*D*) hemorrhagic bullae, a classic NSTI "hard sign." (*E*) Ischemic and superimposed infected necrosis.

are considered systemic inflammatory response syndrome (SIRS) criteria (see **Table 2**). Among the other inflammatory markers, a recent meta-analysis concluded that CRP was slightly superior to ESR and PCT, based on summary area under the receiver operator curve, with a CRP value of 22.5 mg/L maximizing sensitivity and specificity.[35]

Table 3
Differential diagnosis of foot and leg pain and inflammation in a diabetic

Process	Comments
Sensory neuropathy alone	Bilateral; minimal inflammatory signs
PAD alone	Claudication; See text for examination findings
Diabetic (Charcot) neuroarthropathy	Typical x-ray findings
Fracture	Trauma history or acute localized tenderness may be absent owing to sensory neuropathy
Foreign body (eg, pin or tack)	Suggestive history may be lacking owing to sensory neuropathy
Stasis dermatitis	Often bilateral, chronic edema, maximum inflammation above the ankle, hyperpigmentation (brawny edema), warmth redness and tenderness may occur without infection
Gout	Recurrent episodes, first MTP involvement (or history of), pain with minor joint movement
Venous thrombosis	Unilateral edema, often without prominent inflammatory signs

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

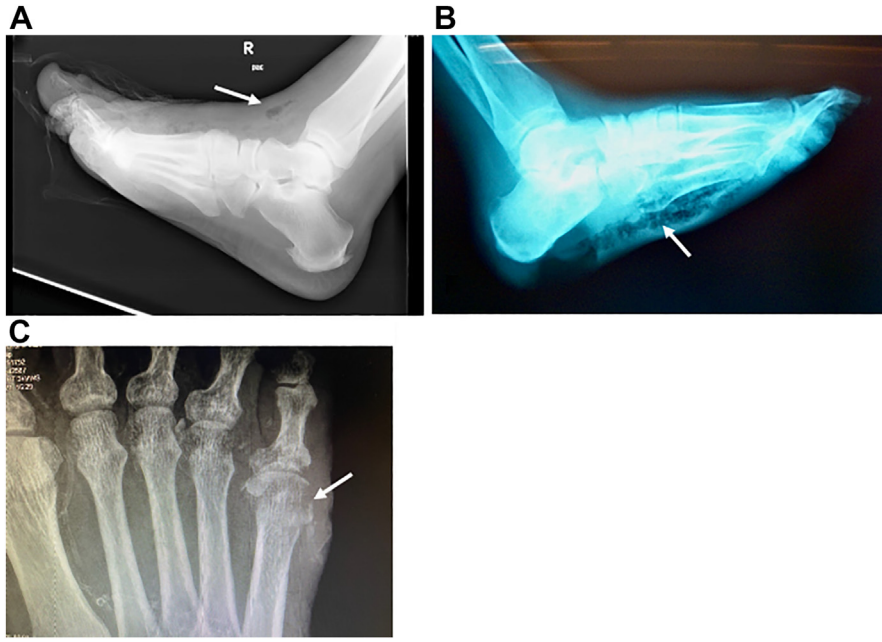

Fig. 6. Plane radiographs. (*A*) Radiograph from patient shown in Fig. 5C, showing soft gas at the level of the ankle (*arrow*). (*B*) Extensive soft tissue gas (*arrow*) along plantar fascia, associated with large hind foot ulcer. (*C*) Osteomyelitis around the fifth metatarsal phalangeal joint, showing cortical erosion and sequestrum (*arrow*).

A 2016 meta-analysis evaluating the performance of biomarkers for the diagnosis of osteomyelitis found that ESR had the highest summary area under the curve, with typical ESR cutoff values in individual studies ranging from 45 to 65 mm/h.[37] The 2019 DFI guidelines promote ESR as the preferred, widely available biomarker for osteomyelitis diagnosis, pointing out that a highly elevated ESR (>70 mm/h) is indicative of bone infection rather than soft tissue infection alone.[12] On the other hand, a 2022 meta-analysis focusing on recent literature found that procalcitonin had the highest summary area under the curve for osteomyelitis diagnosis, with a value of 0.33 ng/mL maximizing sensitivity and specificity, though CRP, ESR, and WBC performed similarly.[35]

The correct and expeditious diagnosis of NSTI relies upon maintaining a high index of suspicion followed by findings present upon immediate operative debridement. "Hard signs" (see earlier discussion) present on physical examination, and imaging results, are likely more important than laboratory findings. Nonetheless, severe hyperglycemia, acidosis—from elevated ketones and/or lactate—and acute kidney injury, should all raise concern for severe DFI, including NSTI. The laboratory risk indicator for necrotizing fasciitis (LRINEC) score was derived and initially touted for its ability to differentiate NSTI from less severe skin and soft tissue infections[38] (**Table 4**). However, a systemic review of subsequent studies (with an unclear proportion of DFI-related cases) found a score of 6 or greater had a summary sensitivity of just 68% and specificity of 84% for NSTI.[31] The only study of the LRINEC score limited to DFIs found that a score of 5 or greater (chosen post-hoc) had sensitivity of 69% and specificity of 52% in predicting the need for amputation—suggesting that LRINEC has a limited role in identifying NSTIs among DFIs.[39]

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 4
Antimicrobial-resistant pathogens often implicated in DFI, their clinical features, and antimicrobials that are typically active against them

Pathogen/Class of Pathogen	Clinical Features	Active Antimicrobials
MRSA (note, more likely when features that predict *S aureus* are present)	Purulent drainage, abscess, prior MRSA isolation, high local MRSA prevalence, and recent hospitalization	TMP-SMX PO Doxycycline PO Linezolid PO or IV Vancomycin Daptomycin
Pseudomonas aeruginosa risk	Prior *P aeruginosa* isolation, macerated wound/ulcer, chronic moisture exposure, and topical climate/ latitude	Ciprofloxacin PO or IV Ceftazidime Piperacillin-tazobactam Imipenem-cilastatin Meropenem
MDR gram-negative bacteria, for example, ESBL-producing *E coli*	Broad spectrum antibiotic therapy or hospitalization in prior 90 d, high prevalence region such as South Asia	Imipenem-cilastatin Meropenem Piperacillin-tazobactam
Obligate anerobic bacteria, for example, *Bacteroides* sp	Necrotic ulcer, deep or chronic ulcer, fetid odor, and limb ischemia with gangrene	Amoxicillin-clavulanate PO Clindamycin PO or IV Moxifloxacin PO or IV Metronidazole PO or IV Ampicillin-sulbactam Piperacillin-tazobactam Imipenem-cilastatin Meropenem

Abbreviations: MRSA, methicillin-resistant *S aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Microbiologic Sampling

Guidelines recommend obtaining a specimen for Gram stain and culture in the "great majority" of DFIs that will undergo antibiotic treatment.[12] In many cases, this responsibility will fall upon the emergency provider, particularly in mild (class 2) infections, where patients are often discharged and started on oral treatment prior to seeing a surgical consultant. The superiority of tissue specimen cultures, as compared to simple swab cultures, has been demonstrated in multiple studies, including a pragmatic outpatient study that showed tissue cultures yielded more true pathogens and more often led to a change in antibiotic treatment.[12,13] In the procedure, after cleansing the surface, a small tissue sample is taken from the wound or ulcer base using sterile forceps and a scalpel, then placed in a sterile container and sent immediately to a microbiology laboratory.[40] For suspected osteomyelitis, it is strongly recommended that surgical or percutaneous bone culture be obtained aseptically by a trained foot surgeon, as soon as possible from the onset of antimicrobial therapy. While preoperative empiric antibiotics are expected to have a limited effect on bone culture yield, whether or not to delay empiric antimicrobials until after bone biopsy in selected cases remains controversial.[12,41]

TREATMENT

Antimicrobial Therapy

The microbiological evidence that underlies therapy recommendations is discussed earlier. The following general points tshould be born in mind when considering empiric antimicrobial therapy for DFI. Microbiologic prevalence and resistance patterns differ between geographic regions and hospital systems, suggesting that empiric therapy regimens should be tailored to local antibiogram data, although this concept has not been studied for DFIs.[42] The general approach now recommended in guidelines is to tailor empiric therapy to infection severity, covering the most common pathogens in all cases (methicillin-susceptible *S aureus* and streptococcal species), with broader parenteral coverage targeting all possible pathogens (MRSA, anaerobes, gram-negative bacteria) reserved for more severe infections.[12] As this practice results in broad-spectrum antibiotic use in many cases, it is critical to obtain proper cultures in the ED to facilitate tailoring of therapy (eg, de-escalation) as soon as possible.

When a true infection is present, systemic antimicrobial therapy is required. Study results do not support the use of topical antimicrobial therapy for foot ulcers or mild DFIs.[12,42,43] There have been only 3 prospective treatment trials with an oral antimicrobial arm.[11,18,44] However, the preference for empiric parenteral therapy both in studies and in practice is not supported by pharmacodynamics; oral cephalosporins, linezolid, quinolones, and other classes are well absorbed and expected to reach effective tissue levels.[9,45] Unfortunately, no studies of nonsevere DFIs have been published yet directly comparing empiric narrow spectrum therapy (oral or parenteral) to broader initial therapy targeting gram negatives and anaerobes.[12] Most of the 21 studies comparing parenteral antimicrobials for DFI have been industry sponsored, comparing various broad-spectrum agents in relatively severe infections, using a noninferiority design. Almost all trials found equivalence, in terms of both safety and efficacy, between the treatment arms. Moreover, meta-analyses have not been able to discern, with a few exceptions, which agents or regimens might be superior.[42,46] At least 9 trials included patients with osteomyelitis and reported osteomyelitis-specific outcomes. Most cases underwent surgical debridement and duration of antimicrobial therapy ranged between 6 and 42 days. Outcomes in these osteomyelitis subgroups also tended to be

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 5
Recommended empiric antimicrobial regimens according to infection severity

		Antimicrobial Choice	Antimicrobial Choice if Confirmed PCN or Beta-lactam Allergy	Other Recommended Agents/Regimens	Comments
Mild (class 2) DFI—oral therapy generally recommended	Nonpurulent	[a]Cephalexin Weight <60 kg: 500 mg PO qid Weight 60–80 kg: 1000 mg PO tid Weight >80 kg: 1000 mg PO qid	[a]Levofloxacin 750 mg PO qid	Dicloxacillin [a]Amoxicillin-clavulanate	Duration 7–14 d
	Purulent/MRSA risk factors	ADD: [a]TMP-SMX 1–2 DS PO bid OR Doxycycline 100 mg PO bid	ADD: [a]TMP/SMX 1–2 DS PO bid OR Doxycycline 100 mg PO bid	Linezolid	
Moderate (class 3) DFI—IV therapy usually required initially	Nonpurulent	[a]Ampicillin-sulbactam 1.5 g IV q 6 h	[a]Levofloxacin 750 mg IV q 24 h PLUS Metronidazole 500 mg IV q 8 h	Moxifloxacin	Obtain tissue culture (see Microbiologic Sampling)
	Purulent/MRSA risk factors	ADD: [a]Vancomycin 20 mg/kg IV loading dose, then 15 mg/kg q 12 h (renal adjustment)	ADD: [a]Vancomycin 20 mg/kg loading dose, then 15 mg/kg q 12 h (renal adjustment)	Linezolid [a]Daptomycin	If oral therapy, duration 14 d
	Oral therapy	[a]Amoxicillin-clavulanate 750 mg PO bid × 14 d; for purulent/MRSA risk factors, add TMP-SMX OR doxycycline, as above		[a]Ciprofloxacin PLUS clindamycin	

(*continued on next page*)

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 5
(*continued*)

	Antimicrobial Choice	Antimicrobial Choice if Confirmed PCN or Beta-lactam Allergy	Other Recommended Agents/Regimens	Comments
Severe (class 4) DFI—immediate IV broad-spectrum antibiotics	[a]Piperacillin-tazobactam 4.5 g IV q 6 h PLUS [a]Vancomycin IV as above	[a]Levofloxacin PLUS metronidazole PLUS [a]vancomycin, as above	[a]Imipenim-cilastin [a]Meropenem [a]Ciprofloxacin OR [a]ceftazidime PLUS metronidazole To all the above, add [a]vancomycin OR linezolid OR [a]daptomycin	Strongly consider immediate surgical consultation for urgent debridement and source control

[a] Renal dosage adjustment may be required.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

equivalent between antimicrobial treatment arms, with no clear preferred agent emerging from the meta-analyses.[42,46]

DFI guidelines published in 2020 use the IWGDF/IDSA classification (see **Table 2**) to define severity and guide empiric antimicrobial selection. Additionally, guidelines and most experts recommend considering various clinical factors not contained in the IWGDF/IDSA classification, which may predict the risk of resistant pathogens; these are listed in **Table 4**. Unfortunately, since there is little trial evidence supporting one antimicrobial agent over another for DFIs, the guidelines lack specific empiric antimicrobial therapy recommendations. **Table 5** lays out a guideline-concordant approach, with one set of empiric antimicrobial choices presented in detail.

Surgical Treatment

Assessing the need for surgical treatment and source control should go hand in hand with antimicrobial selection. Most DFIs will require some surgical treatment, ranging from minor bedside debridement or incision and drainage of a purulent collection—which can be performed by emergency providers—to major operative procedures such as bone resection, amputation, or revascularization. Guidelines recommend immediate surgical consultation for severe limb ischemia, extensive ischemic gangrene, deep abscess, or compartment syndrome and suspected NSTI. In selected cases, it is appropriate to delay the procedure up to 72 hours so that it can be performed in an operating room or surgical specialty clinic. For severe DFIs, there is evidence that early (within 8–72 hours) surgical drainage, debridement, or limited amputation leads to a lower rate of eventual major amputation.[47,48]

In the case of suspected NSTI, numerous studies involving all types of NSTIs have demonstrated that survival and limb salvage are improved in patients who are taken to the operating room within 6 to 24 hours. While there is limited evidence on diabetic foot NSTIs specifically, experience gained from large, single-center case series suggests

Table 6
Factors suggesting that hospitalization is required

Comorbid factors	PAD with severe ischemia Severe venous insufficiency Associated surgical or accidental/traumatic foreign body
Associated systemic illness factors	Rapidly progressive symptoms Fever, hypotension, and confusion Market hyperglycemia, acidosis, and acute kidney injury Marked leukocytosis Markedly elevated inflammatory markers (ESR, CRP, procalcitonin; see Inflammatory Markers)
Local wound and infection characteristics	Rapid progression of swelling and inflammation Extensive cellulitis (>2 cm from ulcer or wound) Lymphangitis Wound penetration to fascia, tendon, muscle, joint, and bone Signs of infectious necrosis: severe pain, crepitus, bullae, and discoloration (see text) Tissue gas located beyond ulcer on x-ray
Additional factors	Need for urgent surgical or diagnostic test not available as outpatient Failure of outpatient management Unable to take oral antibiotics Difficult wound care/dressing changes Complicating psychosocial factors

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

that “early and aggressive” surgical treatment reduces mortality and need for major amputation and limb loss.[48] DFI guidelines recommend that when NSTI is suspected, surgical exploration and debridement or amputation be “urgent” or within 48 hours.[16,29]

Interestingly, the need for routine surgical debridement (vs antimicrobial therapy alone) for osteomyelitis is controversial. Three small studies seem to show that surgical removal of infected bone is not routinely required for nonischemic, forefoot osteomyelitis.[42]

Disposition

Most moderate and all severe DFIs require hospitalization and intravenous antimicrobial therapy. Factors to consider in deciding on disposition are listed in **Table 6**. If the patient will not be admitted directly to a surgical service, consultation with a foot (podiatric, orthopedic, or general) surgeon is mandatory. If there is no other decompensated comorbid illness, mild DFIs can usually be discharged on oral antibiotic therapy. Close follow up—usually within 48 hours—preferably with a foot surgeon, is strongly advised.

CLINICS CARE POINTS

- A careful, well-lit inspection of the feet is mandatory in diabetics presenting with foot pain, unexplained hyperglycemia or unexplained fever or sepsis.
- Infection severity can be assessed using the IWGDF/IDSA classification scheme, based on infection depth and systemic inflammatory signs.
- A critical goal of the physical examination in DFI is to detect signs of a rapidly progressive, limb-threatening NSTI.
- Diabetic osteomyelitis is assessed with the probe to bone test in combination with plain x-ray and inflammatory markers, such as ESR.
- Empiric antimicrobial therapy should be tailored to infection severity; choose oral antimicrobials active against *S aureus* and *Streptococcus* for superficial infections without systemic signs, and a parenteral regimen active against MRSA, gram-negative bacteria, and anaerobes for severe infections.
- Surgical debridement and source control is usually required for an effective treatment of severe DFIs.

DISCLOSURE

Dr B.W. Frazee has no relevant commercial or financial conflict of interest or funding source.

REFERENCES

1. Skrepnek GH, Mills JL, Sr , et al. A Diabetic Emergency One Million Feet Long: Disparities and Burdens of Illness among Diabetic Foot Ulcer Cases within Emergency Departments in the United States, 2006-2010. PLoS One 2015;10(8):e0134914.
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med 2017;376(24):2367–75.
3. Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabet Med 2018;35(1):78–88.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

4. Tan T-W, Shih C-D, Concha-Moore KC, et al. Disparities in outcomes of patients admitted with diabetic foot infections. PLoS One 2019;14(2):e0211481.
5. Lavery LA, Hunt NA, Ndip A, et al. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care 2010;33(11):2365–9.
6. Gardner SE, Hillis SL, Heilmann K, et al. The Neuropathic Diabetic Foot Ulcer Microbiome Is Associated With Clinical Factors. Diabetes 2013;62(3):923–30.
7. Johani K, Fritz BG, Bjarnsholt T, et al. Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches. Clin Microbiol Infect 2019;25(3):332–9.
8. Lavery LA, Armstrong DG, Wunderlich RP, et al. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care 2003;26(5):1435–8.
9. Uçkay I, Aragón-Sánchez J, Lew D, et al. Diabetic foot infections: what have we learned in the last 30 years? Int J Infect Dis 2015;40:81–91.
10. Lew DP, Waldvogel FA. Osteomyelitis. Lancet 2004;364(9431):369–79.
11. Lipsky BA, Pecoraro RE, Larson SA, et al. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Arch Intern Med 1990;150(4):790–7.
12. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev 2020;36(Suppl 1):e3280.
13. Nelson A, Wright-Hughes A, Backhouse MR, et al. CODIFI (Concordance in Diabetic Foot Ulcer Infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. BMJ Open 2018;8(1):e019437.
14. Senneville E, Melliez H, Beltrand E, et al. Culture of Percutaneous Bone Biopsy Specimens For Diagnosis of Diabetic Foot Osteomyelitis: Concordance With Ulcer Swab Cultures. Clin Infect Dis 2006;42(1):57–62.
15. Zenelaj B, Bouvet C, Lipsky BA, et al. Do diabetic foot infections with methicillin-resistant Staphylococcus aureus differ from those with other pathogens? Int J Low Extrem Wounds 2014;13(4):263–72.
16. Lipsky BA. Medical Treatment of Diabetic Foot Infections. Clin Infect Dis 2004;39(Supplement_2):S104–14.
17. Uckay I, Gariani K, Pataky Z, et al. Diabetic foot infections: state-of-the-art. Diabetes Obes Metab 2014;16(4):305–16.
18. Graham DR, Talan DA, Nichols RL, et al. Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. Clin Infect Dis 2002;35(4):381–9.
19. Lipsky BA, Armstrong DG, Citron DM, et al. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 2005;366(9498):1695–703.
20. Hatipoglu M, Mutluoglu M, Turhan V, et al. Causative pathogens and antibiotic resistance in diabetic foot infections: A prospective multi-center study. J Diabetes Complications 2016;30(5):910–6.
21. Rastogi A, Sukumar S, Hajela A, et al. The microbiology of diabetic foot infections in patients recently treated with antibiotic therapy: A prospective study from India. J Diabetes Complications 2017;31(2):407–12.
22. Varaiya AY, Dogra JD, Kulkarni MH, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in diabetic foot infections. Indian J Pathol Microbiol 2008;51(3):370–2.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

23. Charles PG, Uçkay I, Kressmann B, et al. The role of anaerobes in diabetic foot infections. Anaerobe 2015;34:8–13.
24. Rayman G, Vas PR, Baker N, et al. The Ipswich Touch Test: a simple and novel method to identify inpatients with diabetes at risk of foot ulceration. Diabetes Care 2011;34(7):1517–8.
25. Edelson GW, Armstrong DG, Lavery LA, et al. The acutely infected diabetic foot is not adequately evaluated in an inpatient setting. Arch Intern Med 1996;156(20): 2373–8.
26. Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care 2008;31(5):964–7.
27. Monteiro-Soares M, Russell D, Boyko EJ, et al. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). Diabetes Metab Res Rev 2020;36(Suppl 1): e3273.
28. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care 2007;30(3):660–3.
29. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54(12):e132–73.
30. Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA 2008;299(7):806–13.
31. Fernando SM, Tran A, Cheng W, et al. Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physical Examination, Imaging, and LRINEC Score: A Systematic Review and Meta-Analysis. Ann Surg 2019;269(1):58–65.
32. Mandell JC, Khurana B, Smith JT, et al. Osteomyelitis of the lower extremity: pathophysiology, imaging, and classification, with an emphasis on diabetic foot infection. Emerg Radiol 2018;25(2):175–88.
33. Lauri C, Tamminga M, Glaudemans A, et al. Detection of Osteomyelitis in the Diabetic Foot by Imaging Techniques: A Systematic Review and Meta-analysis Comparing MRI, White Blood Cell Scintigraphy, and FDG-PET. Diabetes Care 2017;40(8):1111–20.
34. Senneville É, Lipsky BA, Abbas ZG, et al. Diagnosis of infection in the foot in diabetes: a systematic review. Diabetes Metab Res Rev 2020;36(Suppl 1):e3281.
35. Sharma H, Sharma S, Krishnan A, et al. The efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis: Systematic review and meta-analysis. PLoS One 2022;17(4):e0267412.
36. Armstrong DG, Perales TA, Murff RT, et al. Value of white blood cell count with differential in the acute diabetic foot infection. J Am Podiatr Med Assoc 1996;86(5): 224–7.
37. Victoria van Asten SA, Geradus Peters EJ, Xi Y, et al. The Role of Biomarkers to Diagnose Diabetic Foot Osteomyelitis. A Meta-analysis. Curr Diabetes Rev 2016; 12(4):396–402.
38. Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32(7):1535–41.
39. Sen P, Demirdal T. Predictive ability of LRINEC score in the prediction of limb loss and mortality in diabetic foot infection. Diagn Microbiol Infect Dis 2021;100(1): 115323.
40. Nelson EA, Backhouse MR, Bhogal MS, et al. Concordance in diabetic foot ulcer infection. BMJ Open 2013;3(1).

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

41. van der Merwe M, Rooks K, Crawford H, et al. The effect of antibiotic timing on culture yield in paediatric osteoarticular infection. J Child Orthop 2019;13(1):114–9.
42. Peters EJG, Lipsky BA, Senneville É, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes/Metabolism Research and Reviews 2020;36(S1).
43. Dumville JC, Lipsky BA, Hoey C, et al. Topical antimicrobial agents for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev 2017;6(6):Cd011038.
44. Lipsky BA, Itani K, Norden C. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. Clin Infect Dis 2004;38(1):17–24.
45. Li HK, Agweyu A, English M, et al. An unsupported preference for intravenous antibiotics. PLoS Med 2015;12(5):e1001825.
46. Selva Olid A, Solà I, Barajas-Nava LA, et al. Systemic antibiotics for treating diabetic foot infections. Cochrane Database Syst Rev 2015;2015(9):Cd009061.
47. Faglia E, Clerici G, Caminiti M, et al. The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. J Foot Ankle Surg 2006;45(4):220–6.
48. Tan JS, Friedman NM, Hazelton-Miller C, et al. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? Clin Infect Dis 1996;23(2):286–91.

Descargado para Dr Jorge Martel Granados (emergencymedicine.peru@gmail.com) en Pontifical Xavierian University de ClinicalKey.es por Elsevier en mayo 03, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.